REMARKS

Claims 1-4 were pending in the patent application captioned above. Claims 1-4 were rejected in the Office Action mailed September 30, 2002. The Examiner made the following objections and rejections:

(1) The Examiner objects to the formatting of selected drawings and the figure legend of selected drawings.

(2) The Examiner objects to an informality in a phrase recited in the specification.

(3) Claims 2 and 3 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

(4) Claims 1, 3 and 4 were rejected under 35 U.S.C. 102(b) as being anticipated by U.S. patent 4,762,779 to Snitman. Claims 1-4 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S. patent 6,255,476 to Vinayak *et al.*

(5) Claims 1-4 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. patent 4,762,779 to Snitman in view of U.S. patent 6,255,476 to Vinayak *et al.*

The Applicants respond to and rebut the objections and rejections in the same order presented in the Office Action referenced above.

(1) Applicants Amend The Drawings, In Part.

Applicants have attached, to the instant correspondence, a proposed modification to "Fig. 2B."[1] Specifically, the modification condenses "Fig. 2B" onto one sheet. Applicants submit this proposed modification is sufficient to traverse the objection, raised by the Examiner, regarding the formatting of "Fig. 2B" as originally filed.

The Examiner alleges that, "Figures 1A, 1A(sic), 2A and 2B should be designated by a legend such as --Prior Art-- because only that which is old is illustrated. See, MPEP §608.02(g)."[2] As a threshold objection, the Applicants note the Examiner fails to provide any *specific examples* which illustrate how the reactions, presented in the Figures in question, are identical to anything in the prior art.

The Applicants respectfully disagree that Figures 1A, 1B, 2A and 2B present, exclusively, that which is known in the prior art. Specifically, these figures present embodiments involving the application of Applicants' novel chemistries in various reactions associated with methods for labeling oligonucleotides. For example, the chemistry applied to the Tetramethyl Rhodamine (TMR), used in the reactions recited in Figures 1A and 1B, avoid the unstable acid labile intermediates that are inherent with "standard" labeling techniques described in the prior art.

The reaction scheme, presented in Figures 2A and 2B, project two distinct coupling processes. Figure 2A details the synthesis of the reagents required for this process. Reaction 1 shows the production of a linker phosphoramidite with a base linker molecule. The amino group of the N-methylaminoethanol is first protected as the dimethoxytrityl derivative. In a second reaction, the hydroxyl group is activated toward coupling with the oligonucleotide by conversion into the phosphoramidite. Reaction 2 shows the production of an activated TMR used in the second part of the coupling scheme. The sequential attachment of linker phosphoramidite and activated label is detailed in Figure 2B.[3] The Applicants submit this synthetic scheme is not described by the prior art.

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[1] Pursuant to 37 C.F.R. §1.121 Applicants attach, hereto, a sheet showing the proposed revisions to Fig. 2B in red ink.

[2] Office Action Mailed September 30, 2003, page 2, paragraph 2.

[3] See (in part), page 12, lines 8-16 of the application as filed.

For the reasons elaborated above, therefore, the Applicants decline to label any of the pending figures as "Prior Art." In addition, the Applicants respectfully request the Examiner withdraw his objections, to the Figures, under MPEP §608.02(g).

(2) The Applicants Have Corrected An Informality In The Specification

The Applicants have amended an informality in the specification (cited by the Examiner) on page 9, line 13 of the application originally filed. Specifically, Applicants have amended this section such that it now recites "an activated label." (Emphasis added). Support for this amendment is found in a number of places in the specification[4] including, but not limited to, within the "Definitions" section in the pending application at page 8, lines 17-20. Applicants respectfully request the Examiner withdraw this pending objection to the specification.

(3) The Rejection Under 35 U.S.C. §112 (Second Paragraph) Is Moot

In order to further their business interests, and without acquiescing to the Examiner's arguments (while expressly reserving the right to prosecute the claims as filed or claims similar thereto), the Applicants have: i) canceled claim 2 (while amending claim 1 and claim 4 to incorporate the specific linkers referenced in claim 2) and ii) have incorporated all the specific chemical structures, referenced in the "Tables" recited in claim 3, into the claim itself. Applicants respectfully request the pending rejection to claim 3, under 35 U.S.C. §112 (second paragraph), be withdrawn.

(4) The Claims Are Not Anticipated

It is well settled law that, under 35 U.S.C. §102, anticipation, "requires that each and every element of the claimed invention be disclosed in the prior art. . . . [i]n addition, the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public." *Akzo N.V. v. U.S. International Trade Commission*, 1 USPQ 2d 1241, 1245 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987). Furthermore, "[t]he Examiner bears the burden of presenting at least a *prima facie* case of anticipation." *In re*

[4] Additional support is cited on the next page of this correspondence.

Sun, 31 USPQ 2d 1451, 1453. The Applicants submit the Examiner has failed to make a *prima facie* case of anticipation. That is to say, none of the art cited by the Examiner, in the instant Action, discloses each and every element of the invention as claimed.

A. The Invention as Claimed is Not Anticipated by U.S. Patent 6,255,476 to Vinayak *et al.*

The Examiner states that,

> "Vinayak *et al.* teach labeling an oligonucleotide bound at its 3' end to a polystyrene support by reacting the oligonucleotide with an amino-linker phosphoramidite reagent. The protected amino group is detritylated (thus deprotected) then reacted with an active label, such as TAMRA-CO2H. Other labels taught for use in the method include: 6-FAM, rhodamines and fluoresceins."[5]

The TAMRA label (and indeed all other labels disclosed in the '476 patent to Vinayak *et al.*), are silent on an *unactivated* label which is subsequently reacted, *in situ*, to form an *activated* label. For example, Vinayak *et al.* describe (in Figure 2) an,

> "[E]xemplary route to a labelled-support (ii) where the linker 1 (X-Y-P (1)) is converted to 2 (A-X-Y-P (1)) and attached to aminomethyl, highly-cross linked polystyrene 3. The resulting product 4 is deprotected to 5. ***A pre-activated label, e.g. TAMRA-NHS*** (N-hydroxysuccinimide ester of 5-carboxy tetramethylrhodamine) is covalently attached to 5 to yield the labelled-support 6, ready for oligonucleotide synthesis."[6] (Emphasis added)

In order to further their business, interests and without acquiescing to the Examiner's arguments (while expressly reserving the right to prosecute the claims as filed or claims similar thereto), the Applicants have amended the pending independent claims to highlight one embodiment involving the *in situ* conversion of an unactivated label to an activated label as described by selected embodiments of the present invention. Applicants note this *in situ* conversion step is clearly supported in the application as filed. Specifically, the Applicants stated that:

> "Preparation of a TMR-labeled oligonucleotide as practiced in the current invention is detailed in Figure 3. Conceptually, the approach consists of a novel and empirically discovered modification of the less popular two step

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[5] Office Action mailed September 30, 2002, page 4, paragraph 8.

[6] U.S. Patent 6,255,476 to Vinayak *et al.*, col. 9, lines 19-26.

> procedure such that both reactions are conducted on the solid phase support. In Step 1, the fully protected support-bound oligonucleotide is reacted with linker phosphoramidite and the amino group is deprotected. **In Step 2, the product is reacted with activated TMR, which has been produced *in situ* prior to addition**. Cleavage and deprotection yield the desired oligonucleotide."[7] (emphasis added)

As described above, this *in situ* conversion is specifically highlighted in Figure 3, which identifies an "In Situ-Produced Activated TMR" in the reactions presented. Given that Vinayak *et al.* are silent on the *in situ* conversion to an active label, in a method of labeling oligonucleotides, the reference does not recite each and every element of the invention as presently claimed and, therefore, does not anticipate the pending claims. Applicants respectfully request the pending rejections (under 35 U.S.C. §102(e)) be withdrawn.

B. The Invention as Claimed is Not Anticipated by U.S. Patent 4,762,779 to Snitman

The Examiner admits that, "Snitman does not teach a linker that is identical to the two linkers disclosed in Tables 1, 2 and 3 in the instant application."[8] In order to further their business interests and without acquiescing to the Examiner's arguments (while expressly reserving the right to prosecute the claims as filed or claims similar thereto) the Applicants have amended the pending independent claims to recite the group of linkers defined within Table 1, 2 and 3 of the application as filed. Given the pending claims, now, recite elements the Examiner *admits* are not in the cited reference; Applicants respectfully submit that Snitman *per se* fails to anticipate the invention as claimed. That is to say, since Snitman does not recite each and every element of the invention as claimed, this prior art must fail as a 35 U.S.C. § 102(b) reference.

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[7] See (in part), page 12, lines 25-29 and page 13, lines 1-3 of the application as filed.

[8] Office Action mailed September 30, 2002, page 5, paragraph 10.

(5) The Claims Are Not Obvious Under 35 U.S.C. § 103(a)

A. The Examiner Fails to Make A *Prima Facie* Case of Obviousness

Claims 1-4 stand rejected as allegedly unpatentable over Snitman, in view of Vinayak *et al.*. The Examiner is reminded that a *prima facie* case of obviousness requires citation to a combination of references which (a) disclose the elements of the claimed invention, (b) suggests or motivates one of skill in the art to combine those elements to yield the claimed combination and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of the these three requirements precludes a finding of a *prima facie* case of obviousness, and, without more, entitle the Applicants to allowance of the claims in issue. *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990).

The Applicants respectfully submit the Examiner has failed to establish any of the three elements of a *prima facie* case of obviousness. In addressing this rejection, Applicants focus on independent Claims 1 and 4 since non-obviousness of an independent claim necessarily leads to non-obviousness of claims dependent therefrom. §MPEP 2143.03.

1. No Motivation to Combine the References

A proper analysis, in view of 35 U.S.C. §103, demands the references cited by the Examiner be considered as whole and must suggest the desirability and, thereby, the obviousness of making the combination. *Hodash v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143, n. 5, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicants submits that references cannot be considered collectively until the Examiner points to some motivation to combine said references. This analysis prevents the Examiner from using the instant specification to reconstruct, in hindsight, the invention as claimed. The Federal Circuit has articulated the policy behind this analysis:

> "To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed."

See: *In re Rouffet et al.*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998).

The prior art, referenced above, does not suggest the desirability of making the combination of elements which recapitulates the invention as claimed. In the Office Action mailed on June 6, 1999, the Examiner stated,

> "[a]t the time the invention was made, it would have been obvious to one of ordinary skill[9] in the art to use any moiety at that position that could undergo beta-elimination."[10]

The Applicants respectfully submit the Examiner presents bald conclusions in place of reasoned motivation, as demanded by the Federal Circuit, to combine the cited art.

Specifically the section of the '476 patent to Vinayak *et al.*, cited by the Examiner in the pending rejection under 35 U.S.C. § 103, merely recites a list (e.g. cyanoethyl, methyl, lower alkyl, substituted alkyl, phenyl, aryl, and substituted aryl) of oxygen protecting groups or substituent for the "R" substitution of specific protected-amino phosphoramidites. This alleged teaching by Vinayak *et al.*, however, does not disclose (nor suggest) the advantages offered by the *specific bifunctional linker arms* used in the labeling methods as claimed in the pending application. Despite this shortcoming, the Examiner attempts to fill the void left by the deficient art of Snitman and Vinayak *et al.* with a conclusory argument regarding the alleged "obvious" adaptation of the prior art cited. Specifically, the Examiner sets out the proposition that,

> "the methyl [e.g. the moiety on the phosphate group]is an equivalent of the CH_2CH_2CHN in the prior art. See, for instance col. 11, lines 42-43 of Yinayak *et al.*."[11]

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[9] As a threshold objection, Applicants object submit the Examiner is using a variation of the (discredited) "obvious to try" standard. The Examiner is reminded the CAFC stated, "this court and its predecessors have repeatedly emphasized that 'obvious to try' is not the standard under §103." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). The Examiner is further reminded that, "when the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears." *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). In contrast, the Examiner's alleged "specific reference" to the cited art *fails* to illuminate specific language which *teach the combination of all of the elements* of the invention as claimed.

[10] *Id.*

[11] *Id.*

The *Rouffet* court, however, admonishes against such an unsupported statement. Indeed, the Federal Circuit stated:

> "The Board did not . . . explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination. Instead, the Board merely invoked the high level of skill in the art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technological advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness." *Rouffet*, 47 USPQ2d at 1458.

Contrary to the Examiner's opinion, the prior art provides no motivation to combine the references to teach the claimed invention which describes, in part, the use of *specific bifunctional linker arms* and *in situ activated labels* in methods which produce a labeled support-bound protected oligonucleotide. Accordingly, the rejection of claims 1, 3, and 4, under 35 U.S.C. §103(a) should be withdrawn.

CONCLUSION

The Applicants believe the arguments and amendments, set forth above, traverse the Examiner's rejections and, therefore, requests that all grounds for rejection be withdrawn. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 617.252.3353.

Dated: March 31, 2003

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Registration No. 50,002

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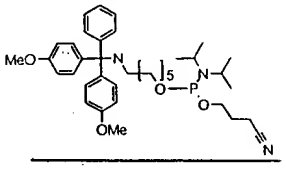
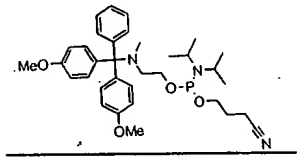
APPENDIX I
MARKED-UP VERSION OF REWRITTEN CLAIMS
PURSUANT TO 37 CFR § 1.121 (c)(1)(ii)

Pending claims 1, 3, and 4 were amended, as follows, in the instant correspondence:

1. A method of labeling oligonucleotides, comprising:

a) providing: i) a solid support-bound oligonucleotide comprising an amino group, ii) a bifunctional linker arm selected from the group consisting of:





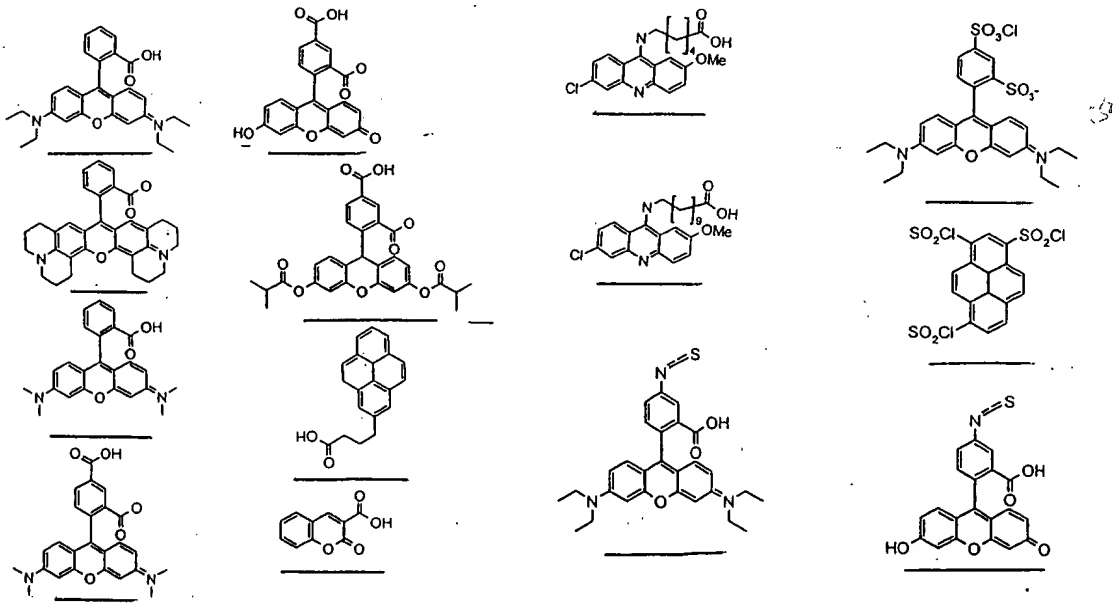
and iii) [an activated label] an *in situ* unactivated label;

b) reacting said solid support-bound oligonucleotide with said bifunctional linker arm to produce a support-bound, linker-oligonucleotide;

c) reacting said *in situ* unactivated label to create an *in situ* activated label; and

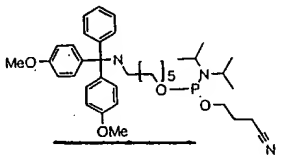
[c)]d) reacting said support-bound linker-oligonucleotide with said activated label to produce a labeled support-bound protected oligonucleotide.

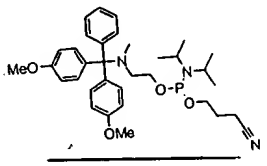
3. The method of Claim 1 wherein said activated label is selected from a group consisting of: [the compounds listed in Table 1, 2 and 3]



4. A method of labeling oligonucleotides, comprising:

a) providing: i) a solid support-bound oligonucleotide comprising an amino group, ii) a bifunctional linker arm selected from the group consisting of:





and iii) an [activated label] *in situ* unactivated label;

b) reacting said solid support-bound oligonucleotide with said bifunctional linker arm to produce a support-bound, protected linker-oligonucleotide;

c) reacting said *in situ* unactivated label to create an *in situ* activated label;

[c)] d) deprotecting the amino group of said support-bound, protected linker-oligonucleotide to produce a support-bound deprotected linker-oligonucleotide, and;

[d)] e) reacting said support-bound deprotected linker-oligonucleotide with said activated label to produce a labeled support-bound protected oligonucleotide.

Appendix III
MARKED-UP VERSION OF REWRITTEN PARAGRAPHS PURSUANT TO 37 C.F.R. § 1.121(b)(1)(iii)

The paragraph beginning on page 9, line 12 and ending on page 9, line 13 was rewritten as follows:

- -Figure 2B shows one embodiment for the attachment of a linker phosphoramidite to an activated label.- -